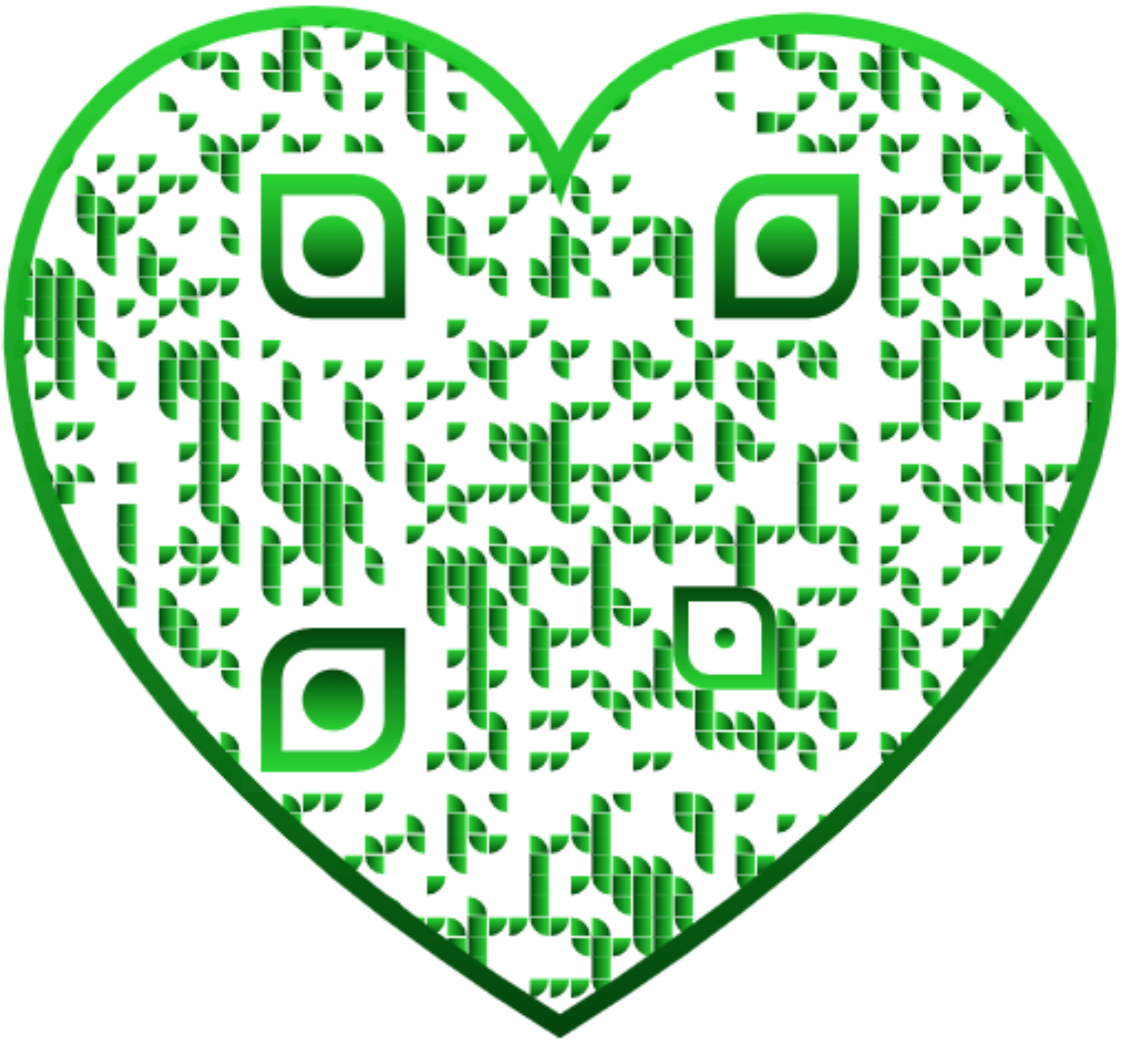
Steroids

Topic outline

- Introduction
- Sources for steroids
- Chemistry and nomenclature of steroids
- Classification and Significance of steroids in pharmacy



I. Introduction

- **Steroids**
  - Are a class of naturally occurring organic substances and their derivatives that are of great importance in biology, medicine, and chemistry
  - are important "biological regulators" that show dramatic physiological effects in living organisms.

Physical properties of steroids

- An important property of steroids is polarty
  - **Steroids are nonpolar**
    - They are soluble in nonpolar organic solvents, e.g. ether, chloroform, acetone and benzene, and
    - Generally insoluble in water
- Slightly soluble in alcohols.

2. Sources of steroids

- Hundreds of steroids have been isolated from plants & animals, and
- Thousands more have been prepared by chemical treatment of natural steroids or by synthesis from simpler compounds.

Sources cont.

- **Natural**
  - Hundreds of distinct steroids have been identified in
    - ✓ plants, animals and fungi, and
  - Most of them have interesting biological activity.
- **Total synthesis**
  - *Is synthesis from simple organic chemicals by reactions that follow known pathways*

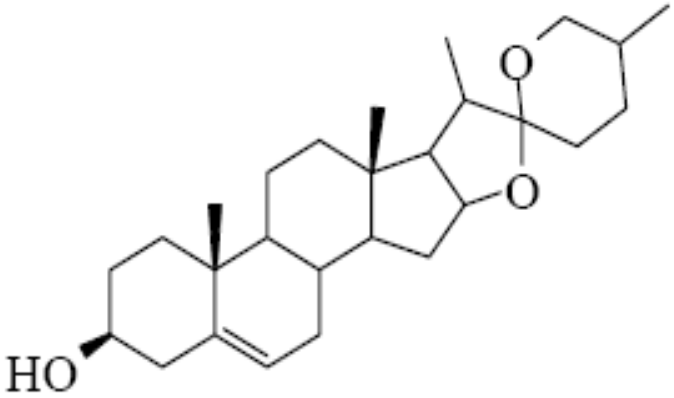
Sources cont.

- Total synthesis of steroids has proved commercially feasible
- Certain microbes can transform parts of the steroid molecule, and
  - industrial steroids are often made by a combination of chemical and microbiological techniques.

Sources cont.

- **Partial synthesis**
  - it is often more practical to prepare steroids by partial synthesis; i.e, ***by modification of other naturally abundant steroids.***
- The bulk of steroid drugs now is manufactured from the abundant ***steroids of plant origin***, notably the ***sapogenins***
- ***Diosgenin***, is typical example of such ***sapogenins***

Sources cont.



Diosgenin

- Obtainable from several varieties of *Dioscorea,* a Mexican yam,
  - Used in the commercial manufacture of **progesterone**, which can be converted
    - To androgenic and estrogenic hormones and
    - To the more complex adrenal steroid hormones, such as cortisone and cortisol

3. Chemistry and biosynthesis

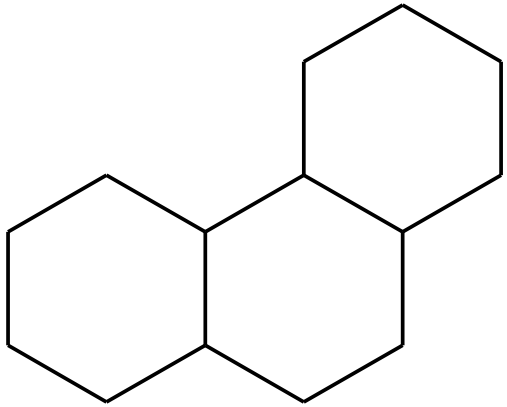
I. Chemistry of steroids

A. Structure

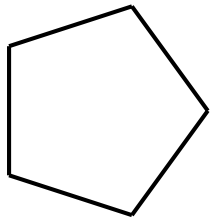
- Structurally, a steroid is a lipid characterized by a carbon skeleton with four fused rings
- Steroids have a common basic ring structures, the cyclopentaphenanthrene ring system (steroid skeleton)

Chemistry – Structure cont.

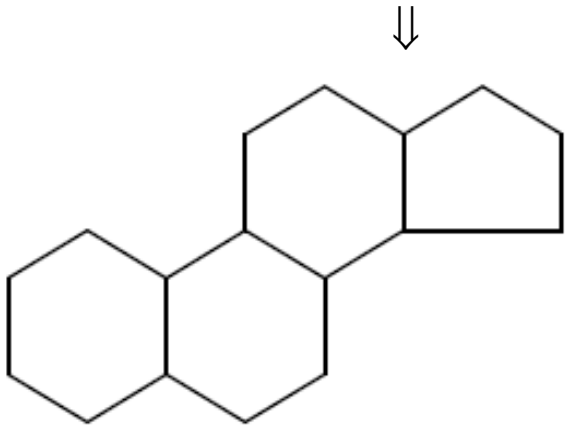
- Cyclopentaphenanthrene ring system (steroid skeleton):
  - ✓ Three-fused cyclohexane rings, phenanthrene part, fused to
  - ✓ a cyclopentane ring



phenanthrene



Cycloprntane



Cyclopentano-perhydrophenantrene

Chemistry – Structure cont.

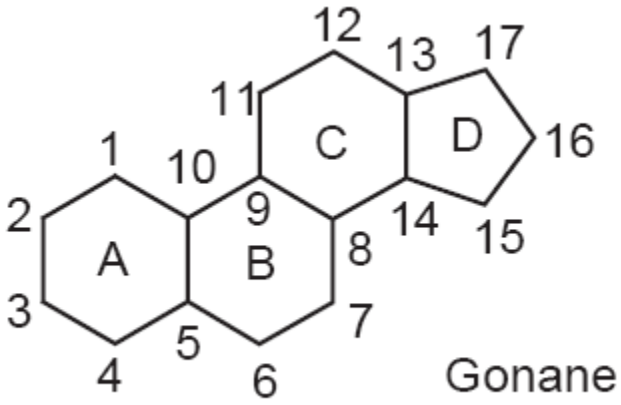
- Steroids vary from one another
  - ✓in the nature of the attached groups,
  - ✓in the configuration of the steroid nucleus and
  - ✓in the position of the attached groups.

Chemistry – Structure cont.

- Small modifications in the molecular structures of steroids can produce
  - ➢ remarkable differences in their biological activities.
- Because of structural similarities, steroids share
  - ✓ Similar chemistry & nomenclature
  - ✓ Common numbering system

Chemistry – Structure cont.

- **Numbering**
  - ✓The four rings are lettered A, B, C and D, and
  - ✓The carbon atoms are numbered beginning in the A ring.
    - This is shown in gonane below.



Gonane

Chemistry – Structure cont.

- Gonane
  - ✓ is the parent structure,
    - ➢ often referred to as the steroid nucleus,
  - ✓ does not occur in nature
  - ✓ may be modified in a practically unlimited number of ways by removal, replacement, or addition of a few atoms at a time.

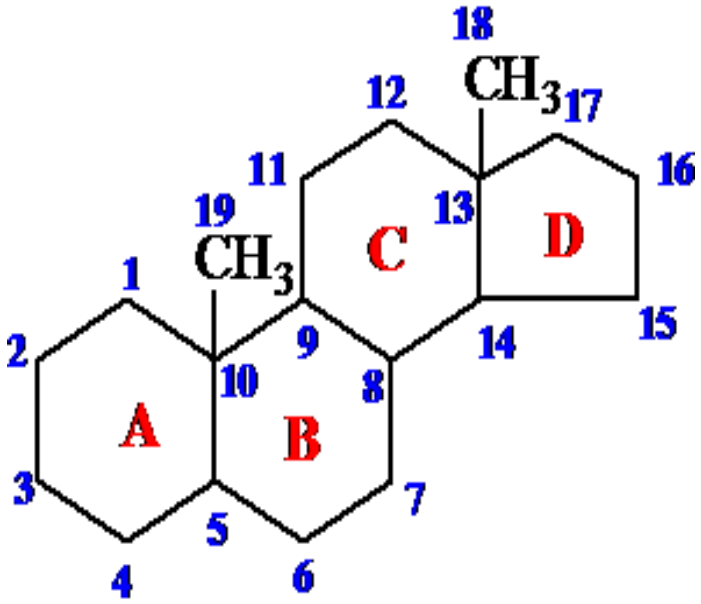
Chemistry – Structure cont.

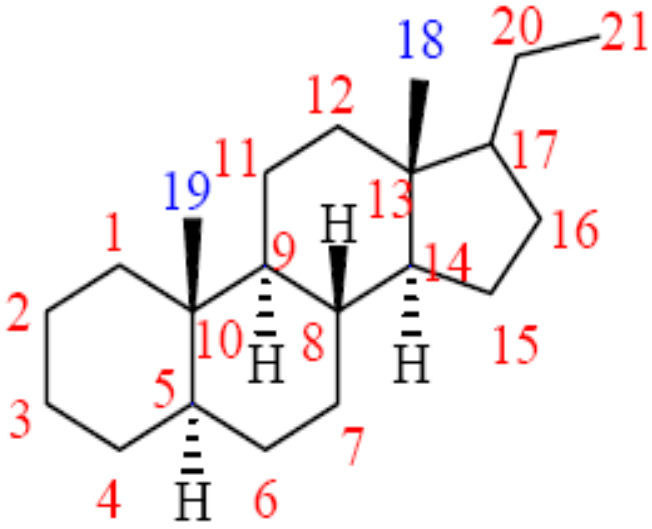
- Each carbon atom of a steroid molecule is numbered, and
  - ✓ the number is reserved to a particular position in the hypothetical parent skeletal structure whether this position is occupied by a carbon atom or not.
- Different steroids vary in the functional groups attached to these rings.

Chemistry – Structure cont.

- All steroids possess at least 17 carbons.
- Many steroids have methyl groups at C-10 and C-13 positions.
  - ✓These are called **angular methyl groups.**
- Steroids may also have a side chain attached to C-17 and
  - ✓a related series of steroids are named after their fundamental ring systems.

Chemistry – Structure cont.



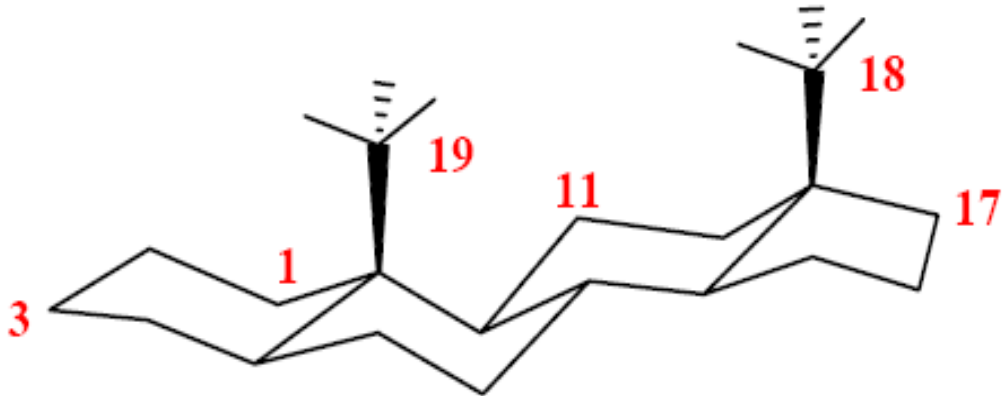


Chemistry – Stereochemistry

B. Stereochemistry of steroids

- ✓ The steroid skeleton shows a specific stereochemistry.
- ✓ All three of the six-member rings can adopt strain-free chair conformations.
- ✓ Unlike simple cyclohexane rings, which can undergo chair–chair interconversions, steroids, being the large rigid molecules cannot undergo ring-flips.

Chemistry – Stereochemistry cont.



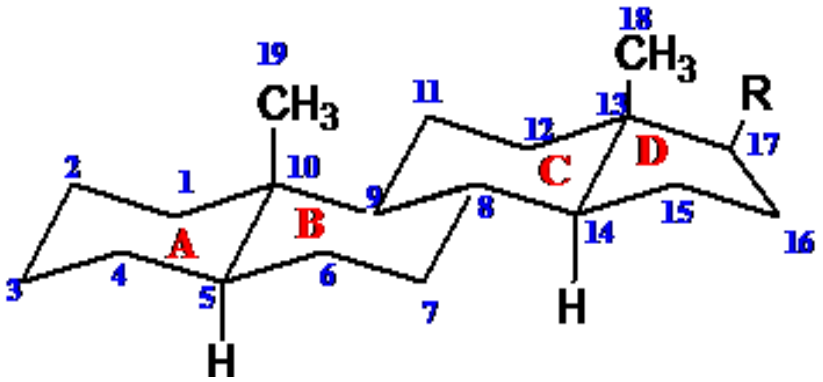
- Although many stereoisomers of this nucleus are possible (and may be synthesized),
  - The saturated nuclear structures of most classes of natural steroids are alike, except at the junction of rings *A* and *B*.

Chemistry – Stereochemistry cont.

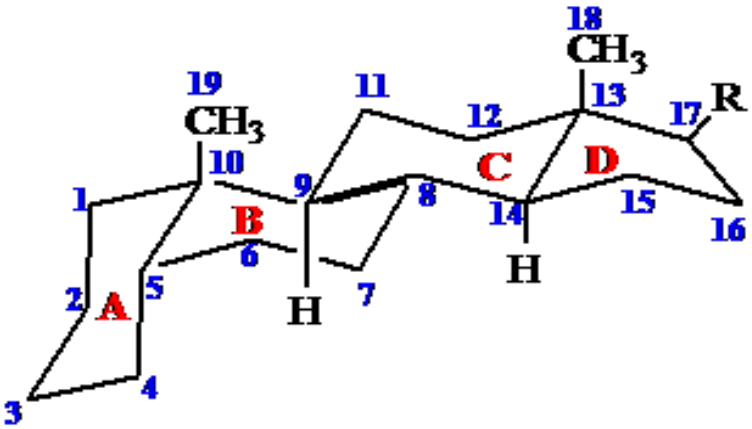
- Steroids can have either *cis* or *trans* fusion of rings A and B;
  - ✓both kind of steroid are relatively long, flat molecules
  - ✓but the A, B trans-fused steroids are by far the more common, though cis-fused steroids are found in bile
  - ✓Thus, in most naturally occurring steroids, rings A and B are *trans* fused.

Chemistry – Stereochemistry cont.

- In most steroids the B, C and C, D ring junctions are *trans*



All ring junctions are *trans*



A, B ring junctions is *cis*

Chemistry – Stereochemistry cont.

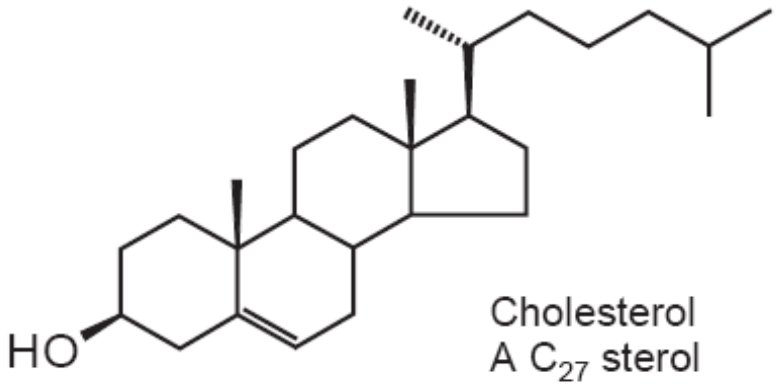
- Substituents on the steroid ring system may be either axial or equatorial, and
  - As usual equatorial substitution is more favorable than axial substitution for steric reasons.
  - Functional groups could vary in reactivity depending on whether they occupied an axial or an equatorial position on a ring.

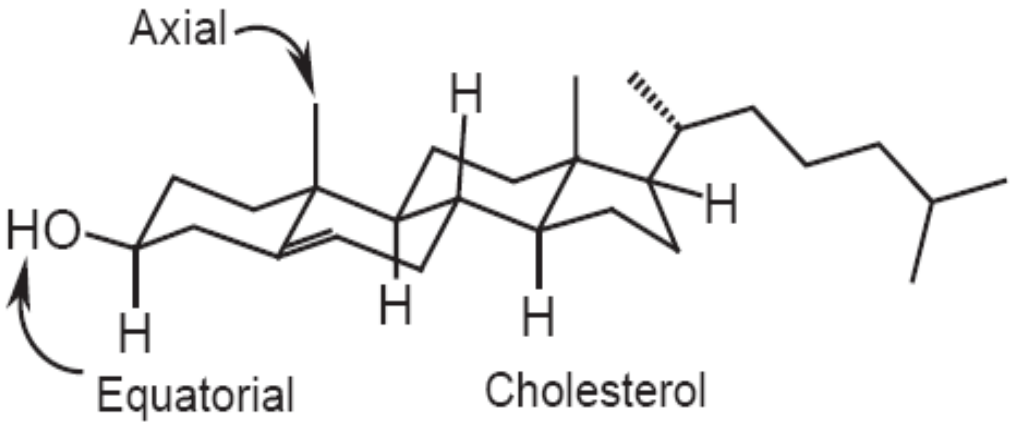
Chemistry – Stereochemistry cont.

- For example, **esters** are
  - formed readily by **3-OH** groups but
  - only with difficulty by the **11β-OH** group

Chemistry – Stereochemistry cont.

- Thus, the hydroxyl group at C-3 of cholesterol has the more stable equatorial orientation





Chemistry – Stereochemistry cont.

- Cholesterol has eight chiral centres, therefore 256 stereoisomers are theoretically possible, but only one exists in nature!

- Similarly, substituents on the steroid ring system may be oriented above or below the plane of the flat molecule
  - The lower side of the steroid is α, the upper side of the steroid is β.

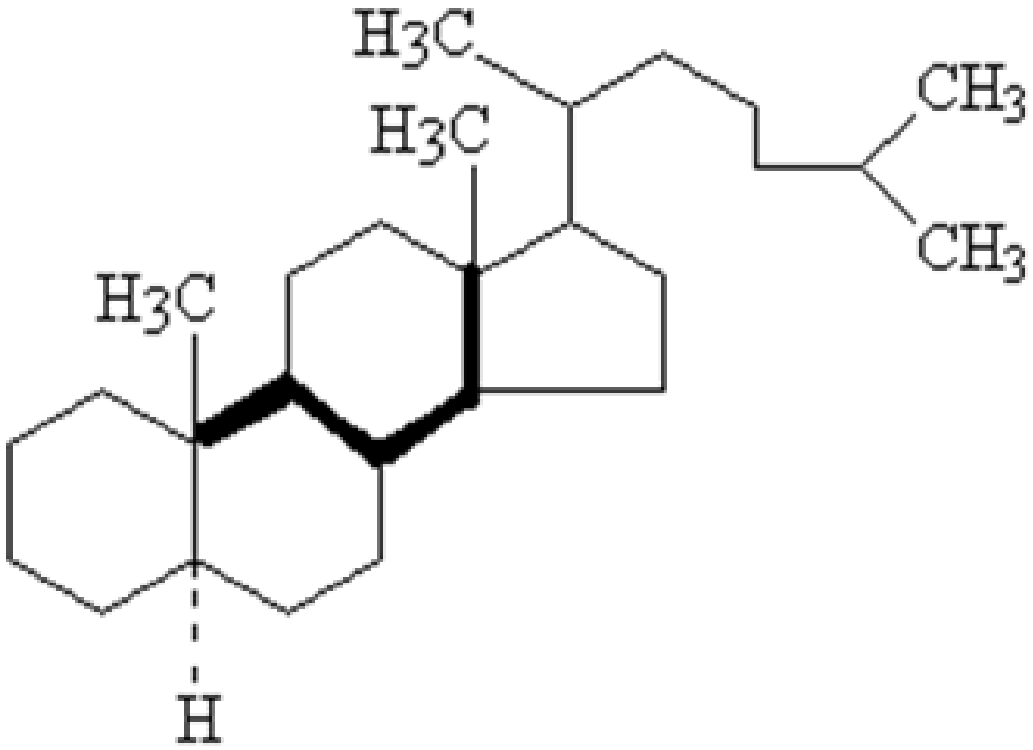
Chemistry – Stereochemistry cont.

- Substituents attached to a saturated (fully substituted) carbon within the steroid ring system are also characterized as α and β.
- Groups attached to unsaturated carbons lie in the same plane as the adjacent carbons of the ring system (as in ethylene), and no orientation need be specified.
- When the orientation of a substituent is unknown, it is assigned the symbol ξ.

Chemistry – Stereochemistry cont.

- The **stereochemistry** of rings A and B must be specified by showing the orientation of the hydrogen atom attached at C5.
  - When α and β designation are applied to the hydrogen atom at position 5,
    - the ring system in which the A, B ring junction is *trans* become the **5α series**; and
    - the ring system in which the A, B ring junction is *cis* becomes the **5β series**

Configuration of H and C-5 is vital and is indicated in the name.



5α–cholestane

Chemistry – Stereochemistry cont.

- Stereogenic centres in steroid side chains are denoted preferentially with the R and S nomenclature.

Chemistry – nomenclature

C. Nomenclature

- In systematic nomenclature(IUPAC),
  - The **R group at position 17** determines the base name of an individual steroid.
  - Steroids are named by modification of the names of skeletal root structures

Chemistry – nomenclature cont.

- The character of substituent groups or other structural modification is indicated by attaching **prefixes** and **suffixes** to the name of the appropriate root structure.
- The prefixes and suffixes include
  - **numbers**, called **locants**, indicative of the position in the carbon skeleton at which the modification occurs, and,

Chemistry – nomenclature cont.

- where necessary, the **orientation** of a substituent is shown as α- or β-.
- for example,
  - ✓ the carbon atom at position 3, is referred to as C3;
  - ✓ a hydroxyl group attached to C3 is referred to as a 3-OH group or, more specifically, as a 3α-OH or 3β-OH group.

Chemistry – nomenclature cont.

- In addition to differences in details of the steroid nucleus,
  - The various classes of steroids are distinguished by variations in the size and structure of an atomic group (the side chain) attached at position 17.

Chemistry – nomenclature cont.

- The derivations of the names of the more common root structures from those of naturally occurring compounds or classes of compounds for which they are most typical are indicated in the Table below.
  - For unambiguous use of these names,
    - the orientation (α or β) of hydrogen at C5 must be specified.

Table: Names of Functional Structures Most Often Used in Steroid Nomenclature			
Name	Carbon atoms present	Naturally occurring general classes	Examples
Gonane	1-17	None	Gonane*
Estrane	1-18	Estrogens	Estradiol
Androstane	1-19	Androgens	Androstane*, testostrone
Pregnane	1-21	Gestogenes and adrenal steroids	Progesterone, cortisol, aldosrone, batrachotoxin
Cholane	1-24	Bile acids	Cholic acid, sodium glycocholate

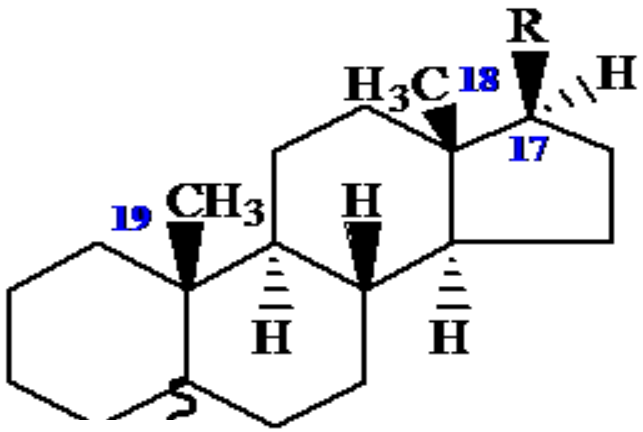
*Gonane and androstane themselves do not occur in nature

Table: Names of Functional Structures Most Often Used in Steroid Nomenclature

Name	Carbon atoms present	Naturally occurring general classes	Examples
Cholestane	1-27	Sterols	Cholesterol,scymnol
Ergostane	1-28	Sterols	Ergosterol, cyasterol
Stigmastane	1-29	Sterols	Stigmasterol, anthridiol
Lanostane	1-27, 30-32	Trimethyl sterols	Lanosterol
Cardanolide	1-23	Cardiac glycosides	Digitoxigenine
Bufanolide	1-24	Toad poisons	Bufatoxicin
Spirostane	1-27	Sapogenins	Dioscin

Chemistry – nomenclature cont.

- The following examples illustrate the way these base names are used.

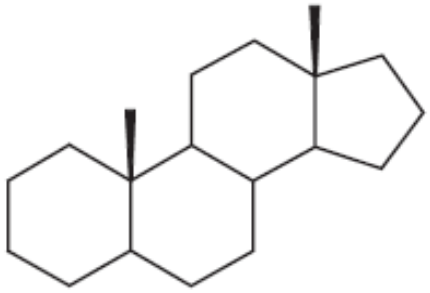


For example: when **R** =

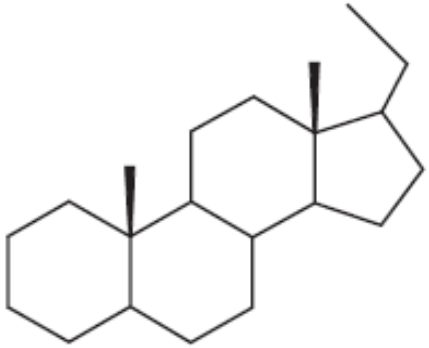
-H ⟶ **Androstane**

-$\overset{20}{C}H_2\overset{21}{C}H_3$ ⟶ **Pregnane**

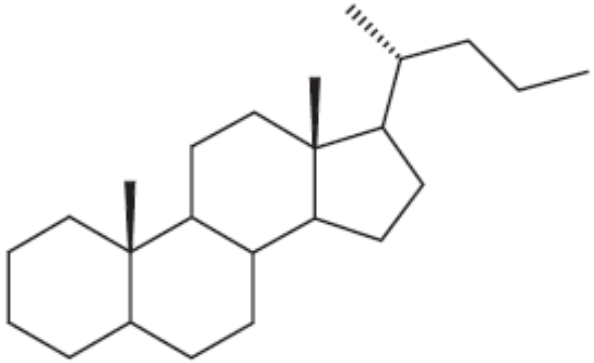
-$\overset{20}{C}H(CH_3)\overset{21}{C}H_2\overset{22}{C}H_2\overset{23}{C}H_2\overset{24}{C}H_3$ ⟶ **Cholane**



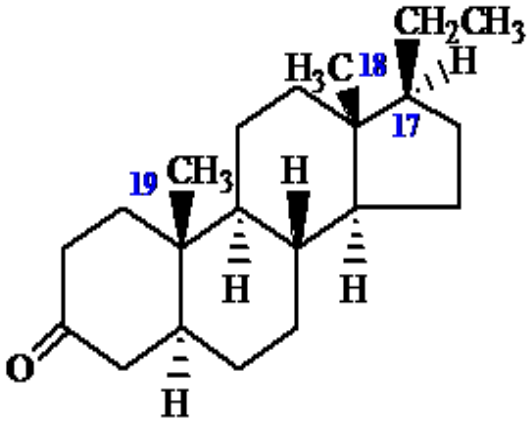
Androstane
A C_{19} steroid



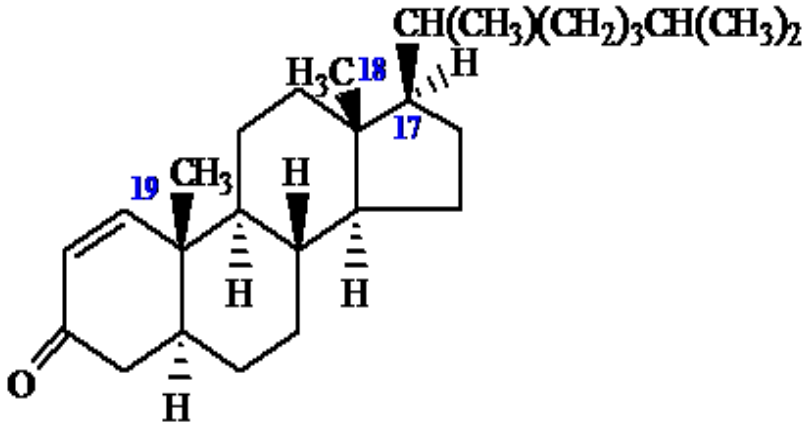
Pregnane
A C_{21} steroid



Cholane
A C_{24} steroid



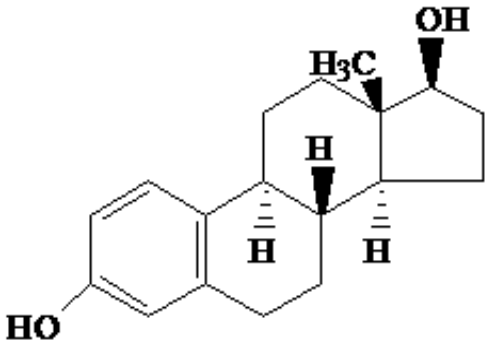
5α-Pregnan-3-one



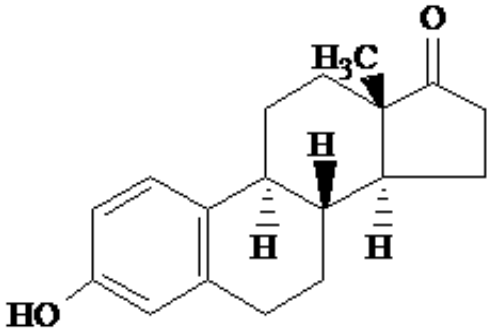
5α-Cholest-1-en -3-one

Chemistry – nomenclature cont.

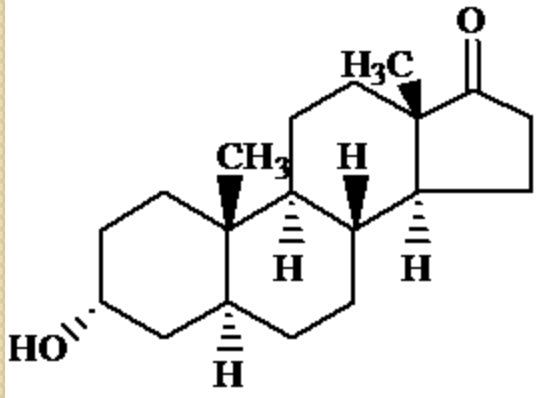
- The following are additional examples of compounds with a steroid nucleus.



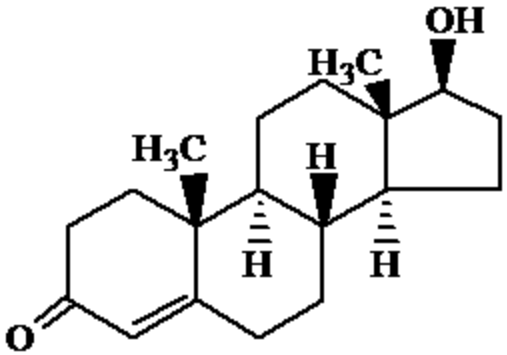
Estradiol



Estrone



Anfrosterone



Testosterone

Chemistry – nomenclature cont.

- In addition to the usual chemical notations for substituent groups replacing hydrogen atoms (*e.g.,* **methyl-, chloro-, hydroxy-, oxo-**), the following prefixes are commonly used:
  - ✓ **dehydro-** lacking two hydrogen atoms from adjacent positions;
  - ✓ **dihydro-** possessing two additional hydrogen atoms in adjacent positions;
  - ✓ **deoxy-** hydroxyl group replaced by a hydrogen atom;

Chemistry – nomenclature cont.

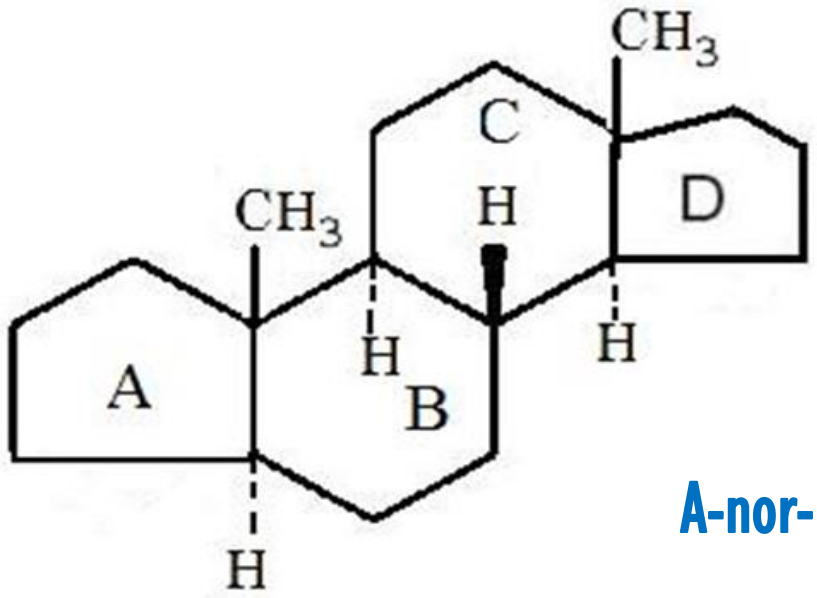
- ✓ **epi-** differing in configuration of a carbon atom bonded to two other carbon atoms;
- ✓ **iso-** differing in configuration of a carbon atom bonded to three other carbon atoms;
- ✓ **nor-** lacking one carbon atom;
- ✓ **homo-** possessing one additional carbon atom;
- ✓ **cyclo-** with a bond between two carbons that are normally not united; and
- ✓ **seco-** with a carbon-carbon bond of the nucleus broken.

Prefix nor is used

a) When a ring is contracted : In this case prefix nor is preceeded by a capital letter indicating the ring affected.

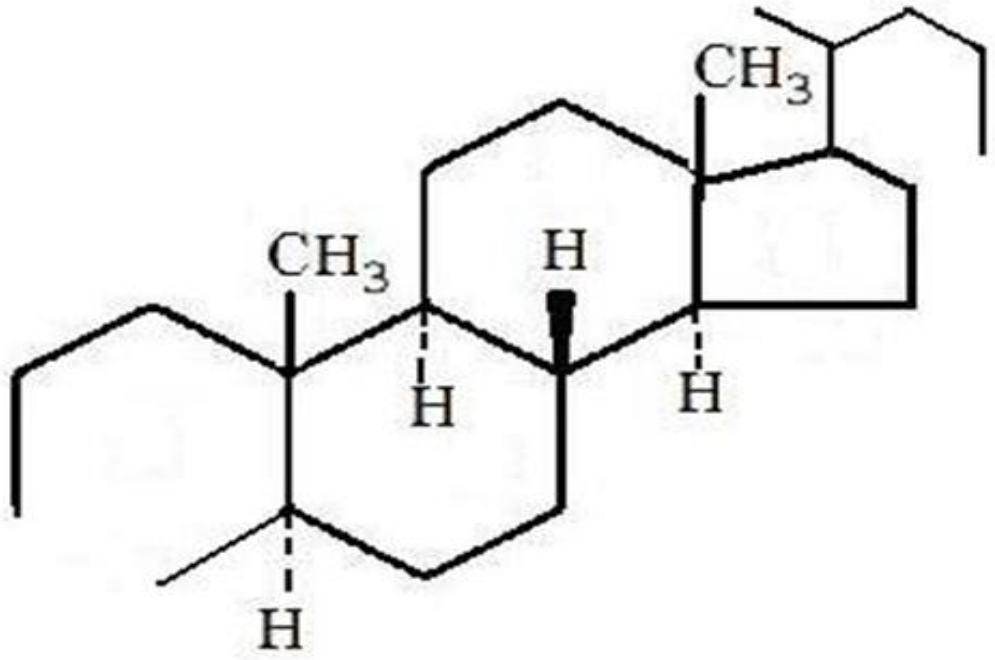
A-nor-5α-androstane

b) To indicate the loss of angular methyl group preceeded by the number designated that methyl group.



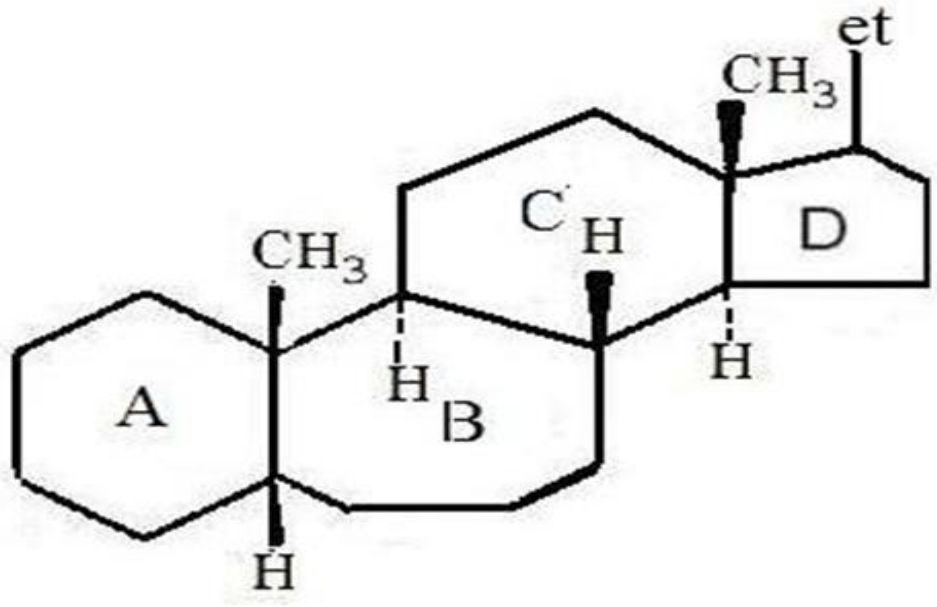
A-nor-5α-androstane

- Prefix *seco*
  - If a carbon-carbon bond of the nucleus broken.



3,4-Seco-5α-Cholane

- ***Homo*** indicates the enlargement of ring. Prefix is preceeded by a capital letter indicating the ring.



B-homo-5β-pregnane

Chemistry and biosynthesis cont.

II. Biosynthesis of steroids

- In plants and animals, steroids appear to be biosynthesized by similar reactions.
- Squalene is thought to be the starting material from which all steroids are made

Biosynthesis cont.

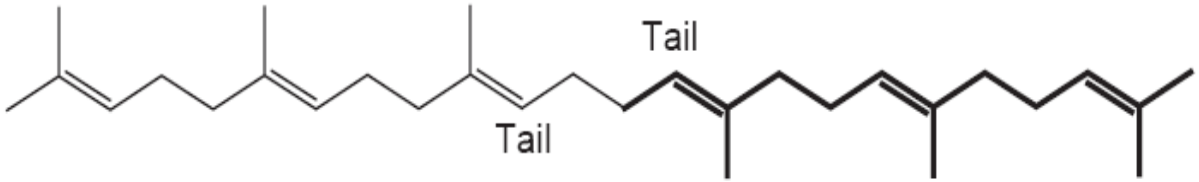
- Enzymatic transformation of squalene produces **lanosterol** in animals and **cycloartenol** in plants, which yield cholesterol in both animals and plants.
- **Squalene** ($C_{30}H_{50}$) is a triterpene, in which the isoprene rule is violated in one point:
  - Rather than a head-to-tail arrangement of six units of isoprene, there appear to be farnesyl units that have been connected tail to tail.

Biosynthesis cont.

- Almost all steroids are biosynthesized from **cholesterol**.
- **Cholesterol** is biosynthesized from **squalene**, which is first converted to **lanosterol.**
  - Squalene is an important biological precursor of many triterpenoids, one of which is cholesterol.

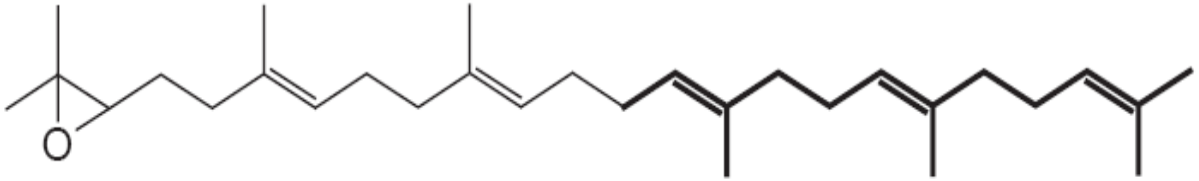
Biosynthesis cont.

- The first step in the conversion of squalene to lanosterol is epoxidation of the 2,3-double bond of squalene to give squalene-2, 3-oxide, and then
  - squalene-2, 3-oxide is transformed by enzymes into lanosterol, and
  - lanosterol in turn is converted to cholesterol by enzymes in a series of 19 steps.
- The whole process is highly stereoselective.



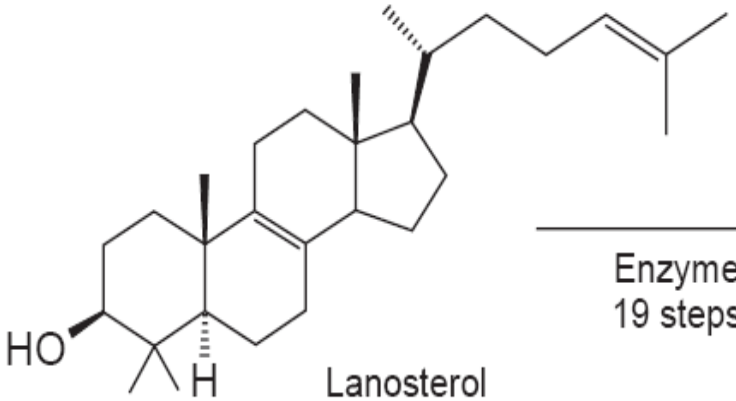
Squalene
Formed from tail-to-tail combination of 2 FPP

O_2 | Squalene epoxidase



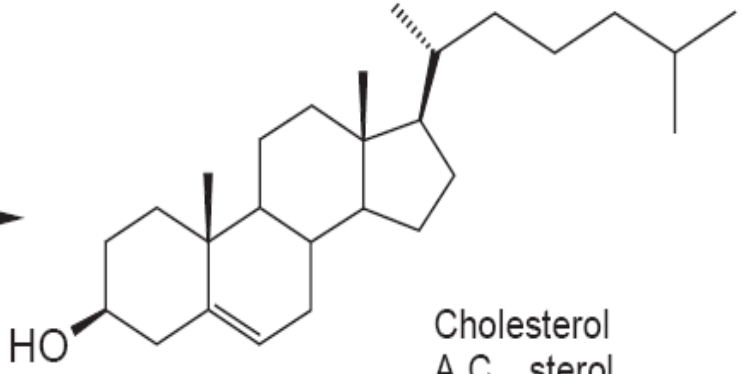
Squalene-2,3-oxide

$-H^+$ | Lanosterol cyclase



Lanosterol

Enzyme
19 steps



Cholesterol
A C_{27} sterol

4. Classification and significance of steroids in pharmacy

- Different categories of steroids are frequently distinguished from each other by
  - names that relate to their **biological source,** e.g
    - ✓ phytosterols (found in plants),
    - ✓ adrenal steroids, and
    - ✓ bile acids or

Classification cont.

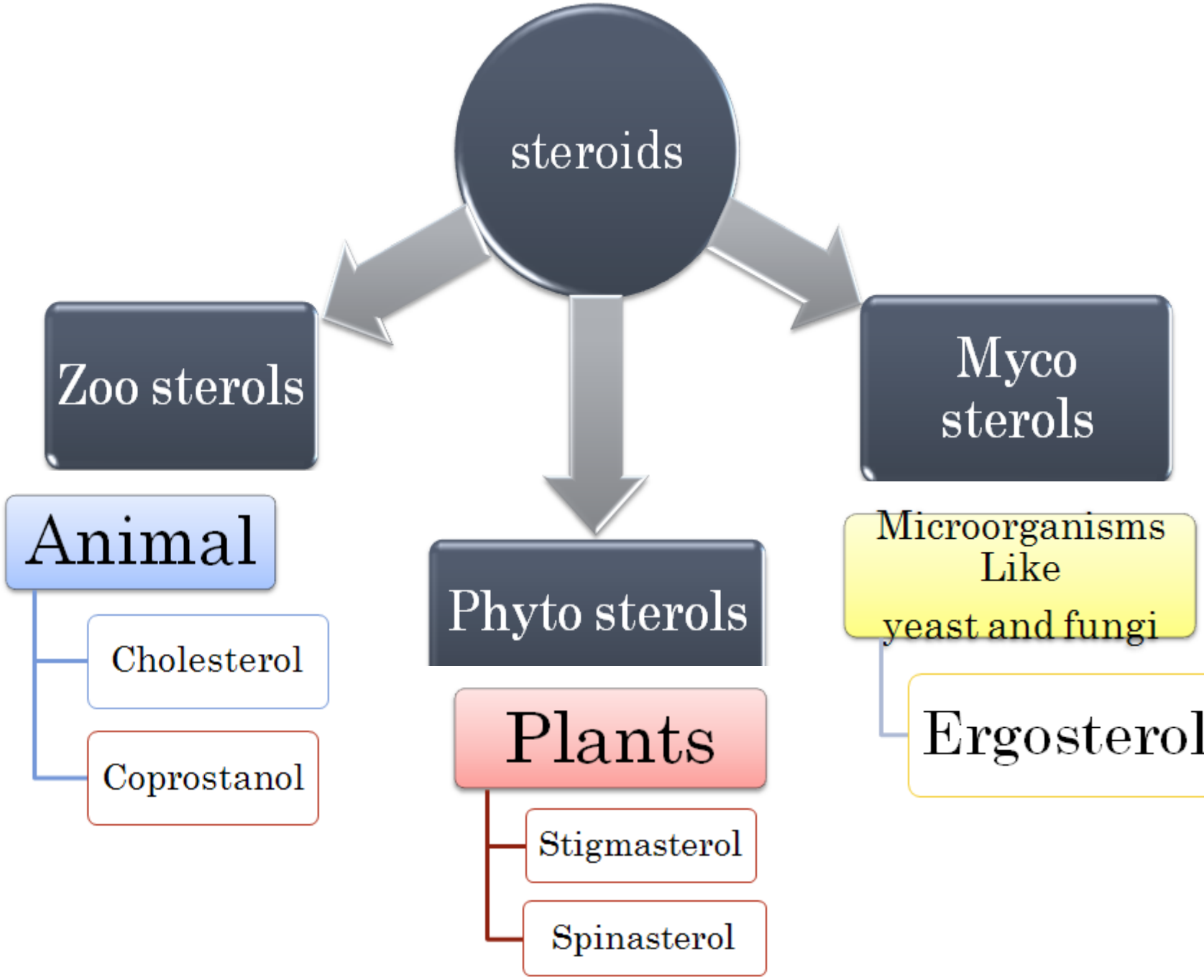
- names that relate to some **important physiological function,** e.g
  - ✓ gestogens (promoting gestation),
  - ✓ androgens (favouring development of masculine characteristics), and
  - ✓ cardiotonic steroids (facilitating proper heart function).

Classification cont.

- Because steroids of similar function and origin tend to fall into families of closely related structure, **biological categorization** underlies an internationally accepted systematic chemical nomenclature.

Classification cont.

- **Classification-based on the source**
  - **Fungus steroids** - Ergosterols
  - **Plant steroids** - Phytosterols
  - **Animal steroids**
    - Insect steroids-Ecdysteroids
    - Vertebrate steroids
      - Corticosteroids - Glucocorticoids/ Mineralocorticoids
      - Sex steroids (Sex hormones) - Androgens/ Estrogens

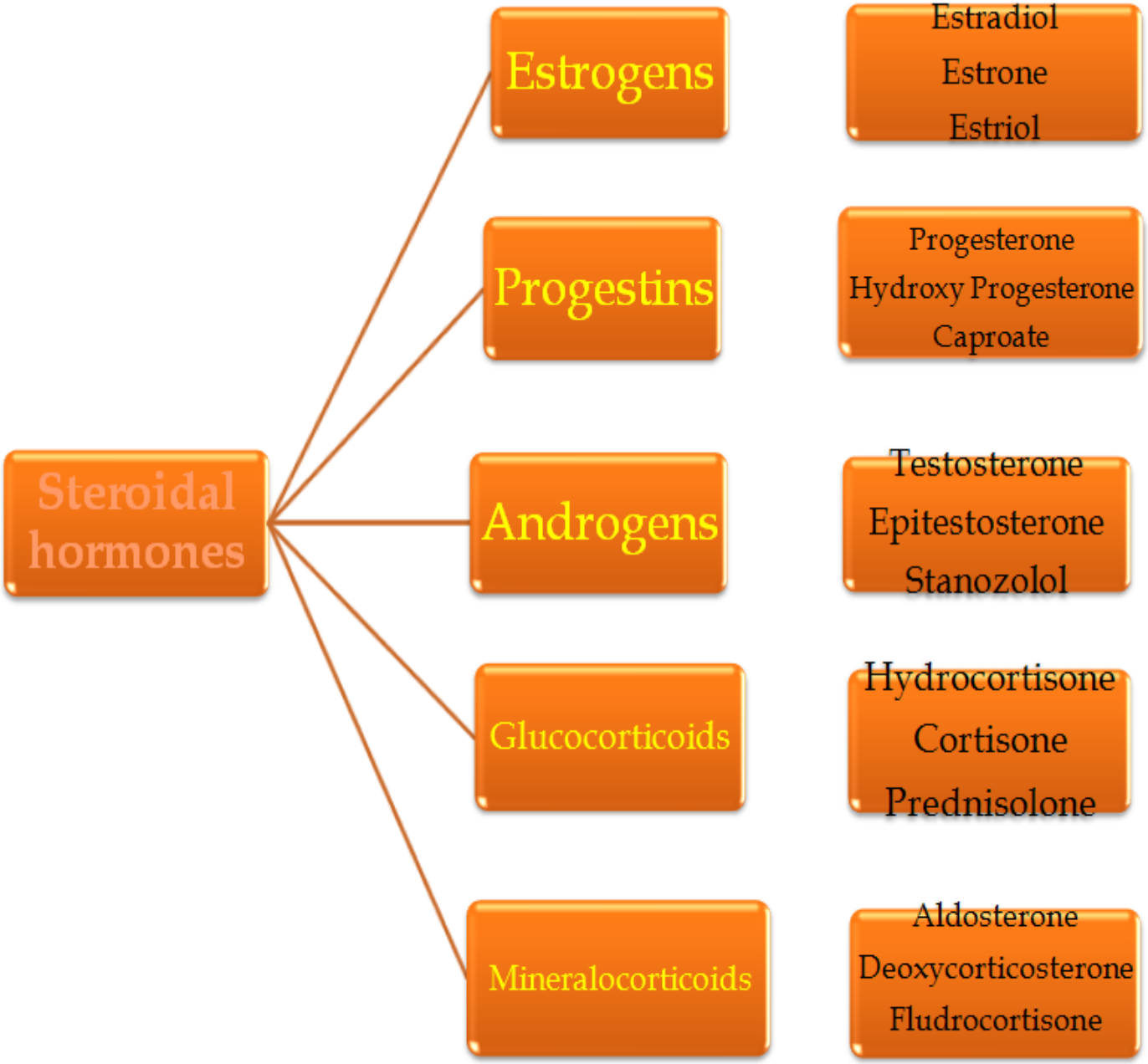

steroids
Zoo sterols
Animal
Cholesterol
Coprostanol
Phyto sterols
Plants
Stigmasterol
Spinasterol
Myco sterols
Microorganisms Like
yeast and fungi
Ergosterol

Classification cont.

- **Classification - based on functional group or physiological function**
  - Sterols (steroid alcohols)
  - Bile acids
  - Cardiotonic steroid glycosides
  - Steroid saponins
  - Sexual hormones:
    - female sex hormones: estrogens, progestins
    - male sex hormones: androgens

Classification cont.

- Hormones of adrenal cortex:
  - glycocorticosteroids;
  - mineralocorticosteroids
- Metamorphosis hormones. Ecdysteroids.
- Steroid alkaloids


Steroidal hormones
Estrogens
Estradiol
Estrone
Estriol
Progestins
Progesterone
Hydroxy Progesterone Caproate
Androgens
Testosterone
Epitestosterone
Stanozolol
Glucocorticoids
Hydrocortisone
Cortisone
Prednisolone
Mineralocorticoids
Aldosterone
Deoxycorticosterone
Fludrocortisone

Classification cont.

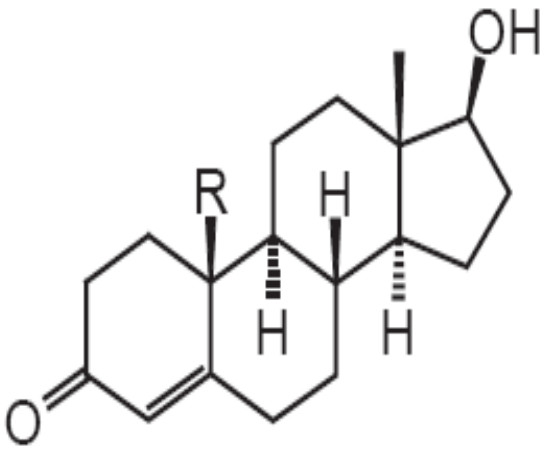
- Steroids exhibited diverse physiological functions and effects
  - Most of the functions, especially those of a hormonal type, involve the transmission of biologically essential information.
  - The specific information content of the steroid resides
    - in the character and arrangement of its substituent groups and
    - in other subtle structural modifications.
  - **Below are examples of some functional classes of steroids**

Classification cont.

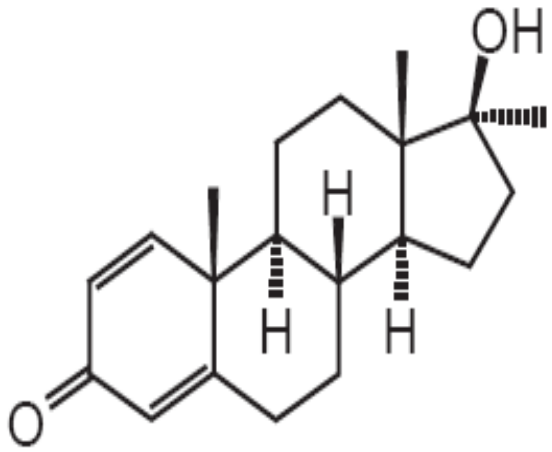
(a) Anabolic steroids

- Interact with **androgen receptors** to promote **cell growth** and **division**, resulting in growth of several types of tissue, especially **muscle** and **bone**
- Examples: testosterone, nandrolone and methandrostenolone

Classification cont.



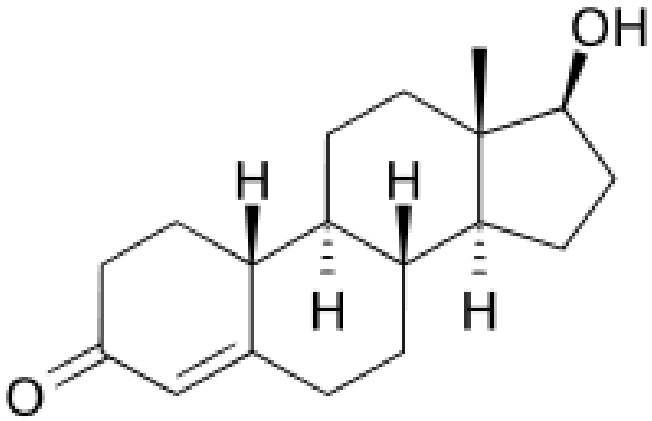
Testosterone R = Me
Nandrolone R = H
Natural anabolic steroids



Methandrostenolone
A synthetic anabolic steroid

Classification cont.

- **Abusing anabolic steroids**
  - Quite frequently, world-class athletes and sports personalities abuse anabolic steroids, e.g.
    - **Nandrolone,** to enhance performance and also to improve physical appearance.

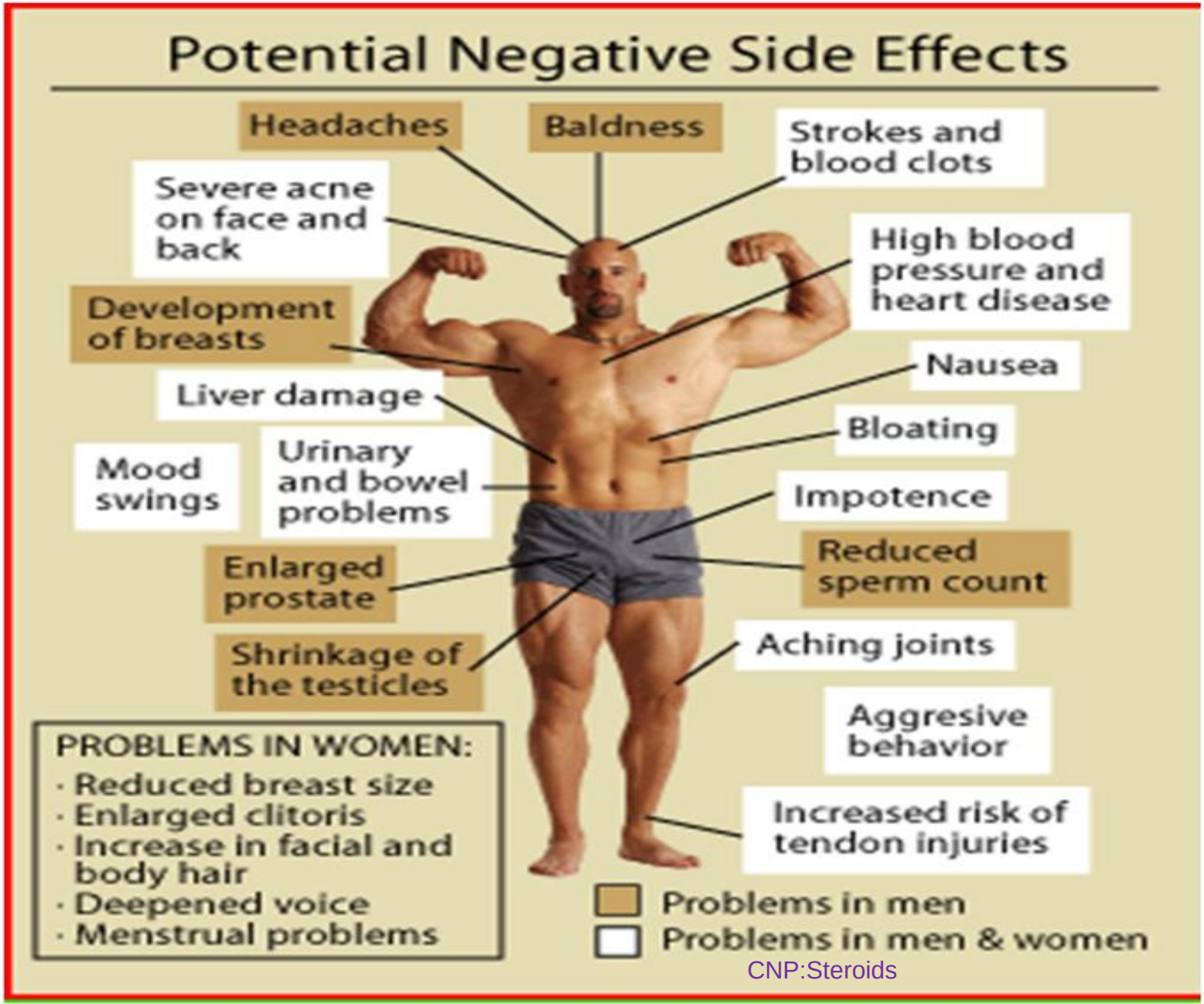


Nandrolone

Abusing anabolic steroids cont.

- Designed to act like testosterone
- Used illegally by athletes
- To enhance performance and/or improve physical performance
- Increases body mass, strength, and power and Decreases body fat
- Banned by most athletic associations
- Anabolic Steroid Control Act of 2004

• STEROIDAL ABUSE



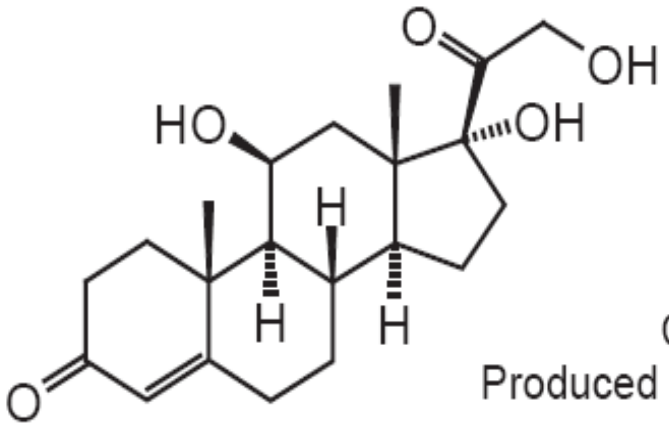
Classification cont.

(b) Corticosteroids

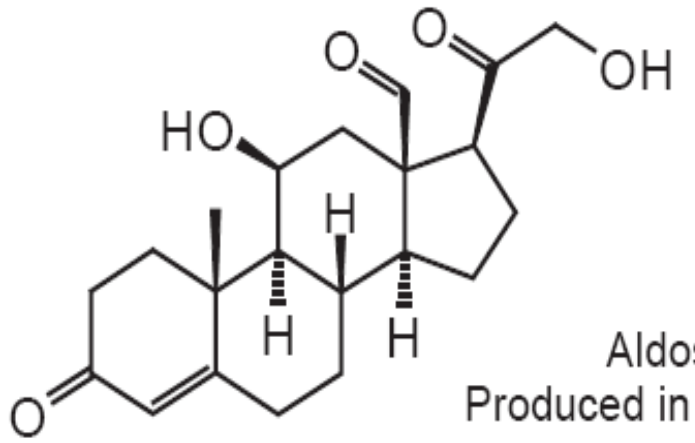
- **Glucocorticoids**
  - Are characterized by an ability to bind with the **cortisol receptor** and trigger similar effects:
    - Regulate many aspects of metabolism and immune functions
  - Are often prescribed as a remedy for inflammatory conditions such as asthma and arthritis.
  - Example: cortisol.

Classification cont.

- **Mineralocorticoids**
  - Are corticosteroids that help maintain blood volume and control renal excretion of electrolytes
  - Example: **aldosterone**



Cortisol
Produced in adrenal cortex



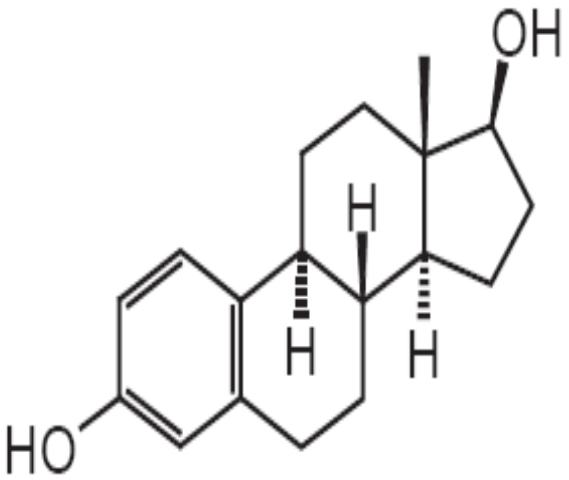
Aldosterone
Produced in adrenal cortex

Classification cont.

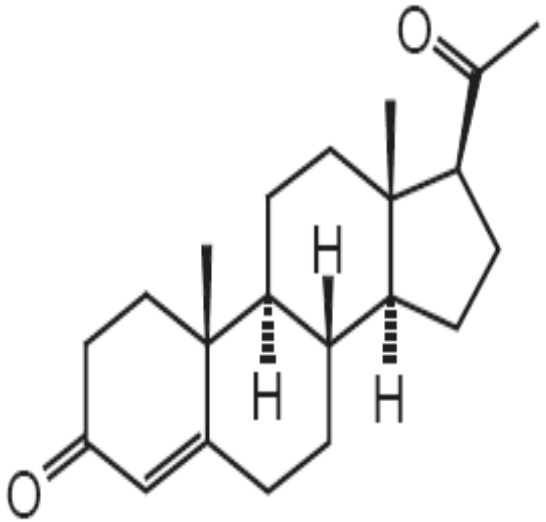
(c) Sex steroids

- Are a subset of sex hormones that interacts with vertebrate **androgen** or **oestrogen** receptors to produce
  - sex differences (primary and secondary sex characters) and
  - support reproduction.
- They include androgens, oestrogens and progestagens.
- Examples: testosterone, oestradiol and progesterone.

Classification cont.

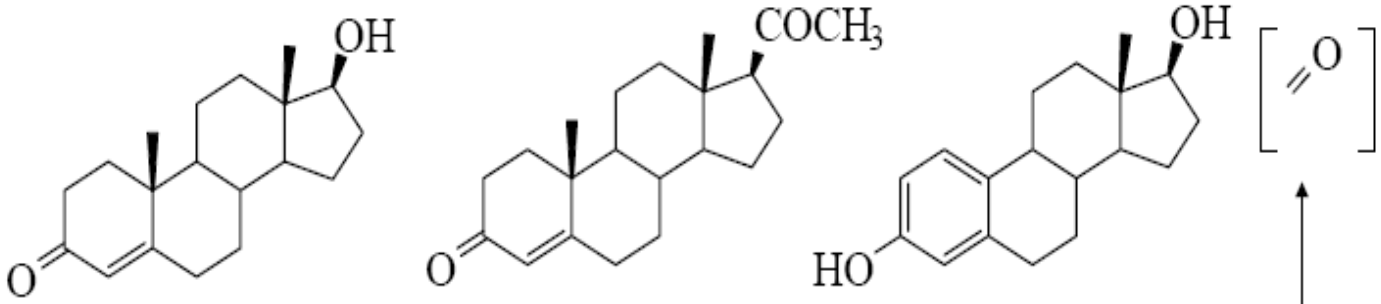


Oestradiol (estradiol)
The major oestrogen in humans



Progesterone
Supports gestation

Classification cont.



Male
[androgen]
Testosterone

Secreted by testes
Controls 2° sex characs
[hair, voice, muscles, sex]

Female
[gestogen]
Progesterone

ovaries
Prepares uterus for pregnancy

Female
[estrogen]
Estradiol
[Estrone]

ovaries
Controls 2° sex chs
[breasts, hair, menstrual cycle]

Classification cont.

(d) Sterols: Cholesterol, Phytosterols, Ergosterols

- The most generally abundant steroids are ***sterols***
- Are present in both plant and animal foods
- Major sterol is **cholesterol**
- **Stigmasterol** is the most common sterol in plants

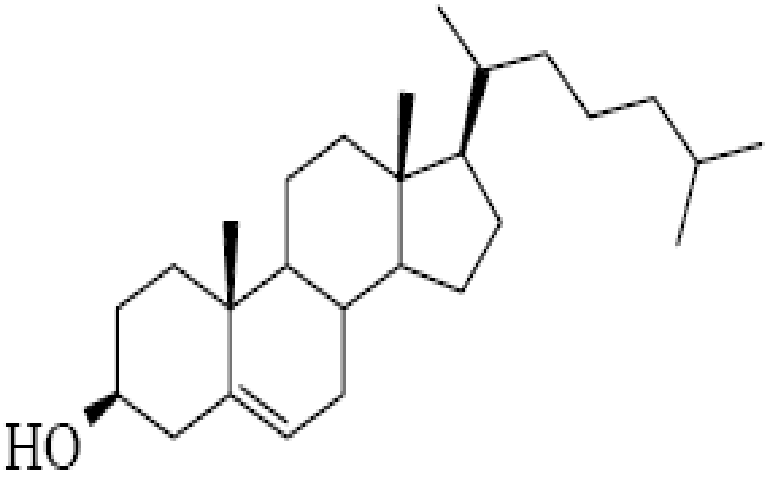
Classification cont.

1. Cholesterol

- Sources – egg yolks, liver, shellfish, organ foods, brain
- Plant and animal food contain sterols but only animal food contain cholesterol
  - Why?
    - Cholesterol is made in the liver and plants do not have a liver

Classification cont.

- Cholesterol
  - serves as a precursor for many other important compounds:
    - It is needed to make bile, sex hormones, steroids and vitamin D, etc.
  - is the constituent of cell membrane structure

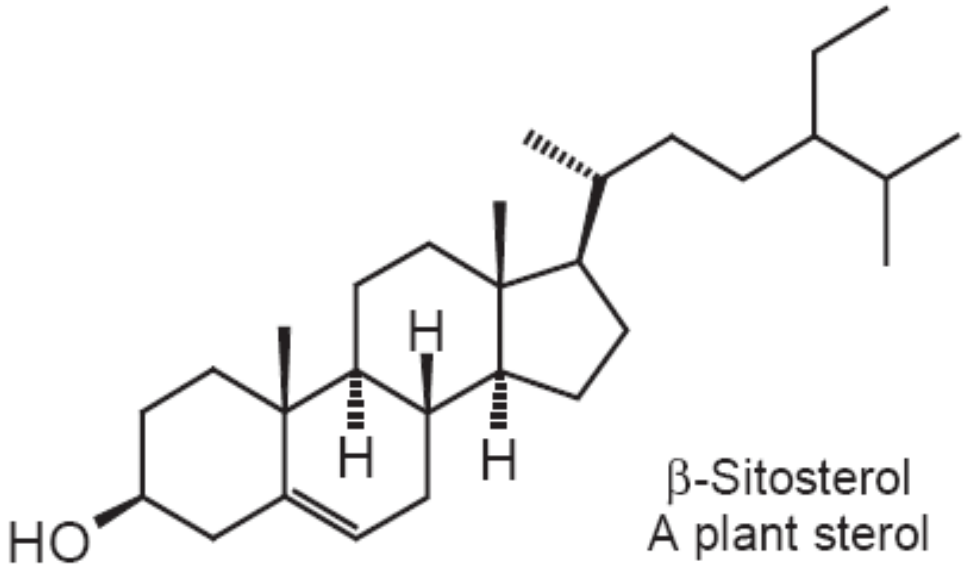


Cholesterol

Classification cont.

2. Phytosterols or plant sterols

- are steroid alcohols that occur naturally in plants.
- Example: β-sitosterol.

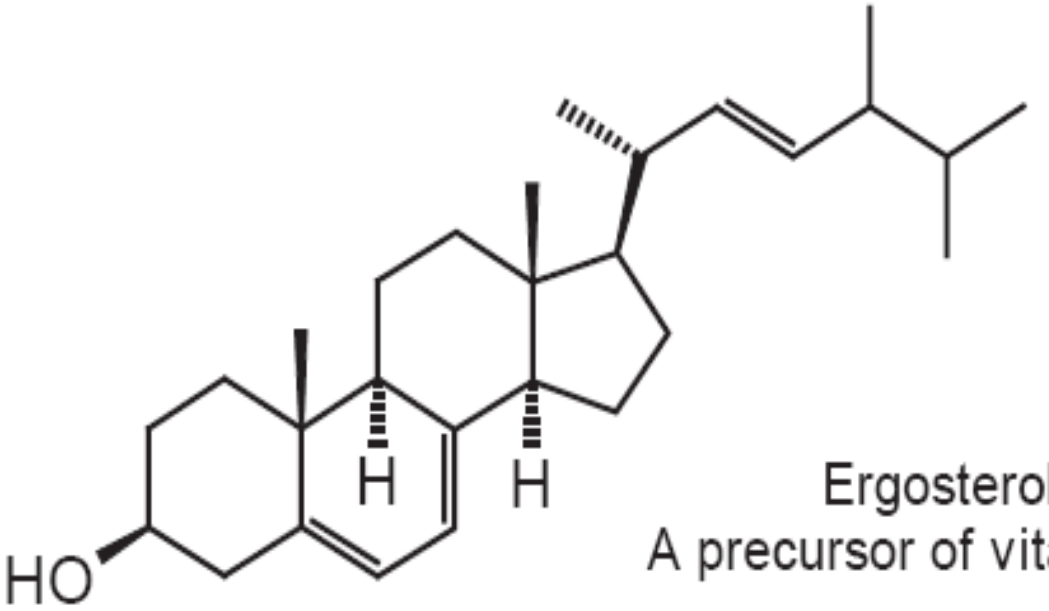


β-Sitosterol
A plant sterol

Classification cont.

3. Ergosterols

- are steroids that occur in fungi, and include some vitamin D supplements.



Ergosterol
A precursor of vitamin D_2

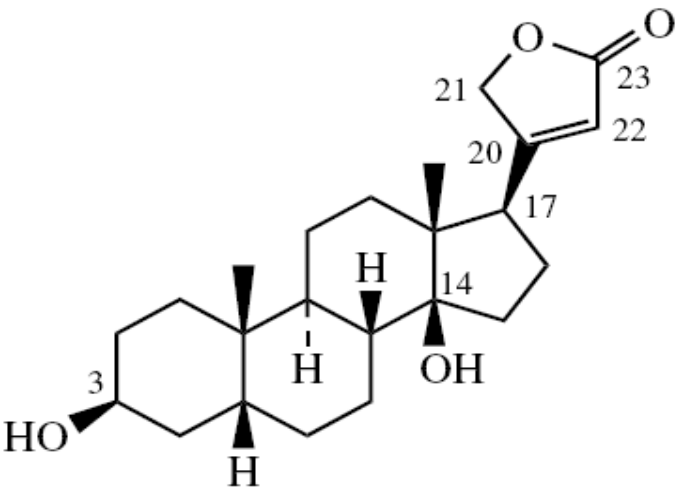
Classification cont.

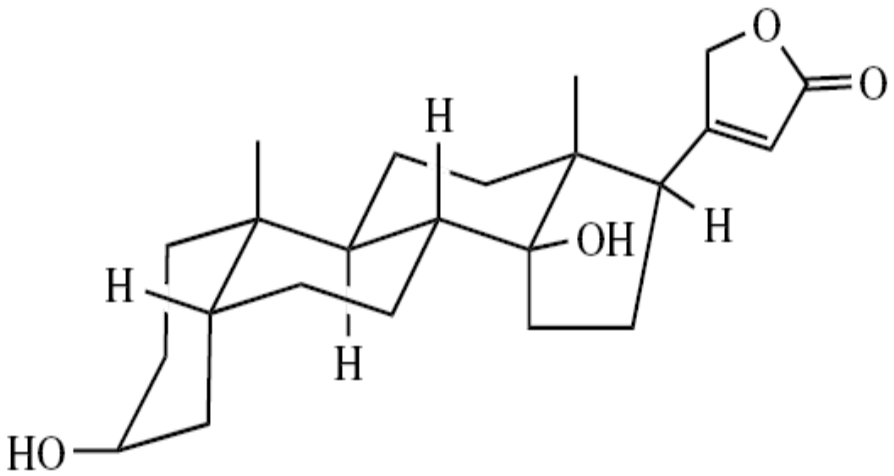
(e) Cardiac glycosides

- Are steroids that have a highly specific and powerful action on cardiac muscle
- Source include *Digitalis purpurea*
- Contain steroid nucleus with its 3-OH in glycosidic form with sugar molecules
  - Agycone (steroid nucleus) has the cardiac activity

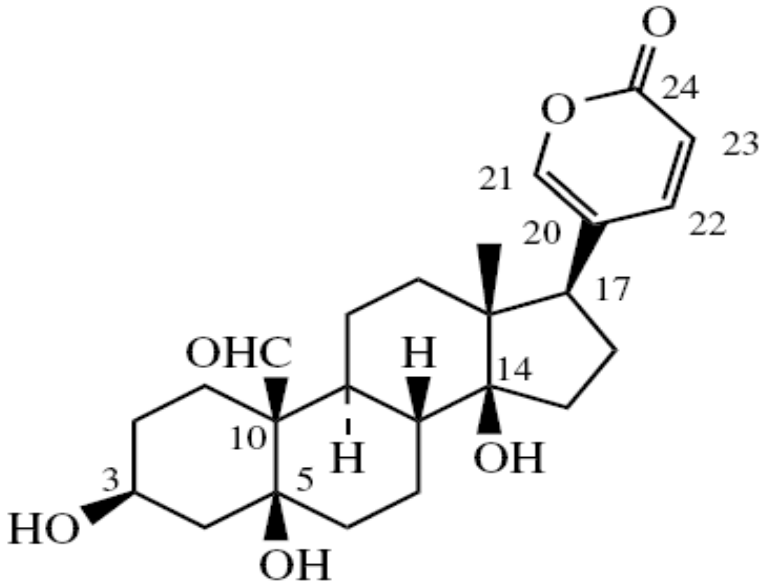
Classification cont.

- Characteristic features of cardiac glycosides:
  - ✓ *Cis-fused* A/B and C/D rings
  - ✓ 14β-hydroxyl
  - ✓ Unsaturated lactone at C-17β
  - ✓ Sugar residues on 3β-hydroxyl
- Based on the size of the lactone ring at C-17β, cardiac glycosides are categorized as
  - ✓ **Cardanolides** (five member ring)and
  - ✓ **Bufanolides** (six member ring)





Cardenolide – digitoxigenin



bufadienolide - hellebrigenin

Classification cont.

f) Bile acids

- The principal forms in which cholesterol is excreted by vertebrates are the **bile acids**
- **Aid in lipid digestion**
- The **bile acids** (cholanoic acids, also called **cholanic acids**) of higher vertebrates form conjugates with the amino acid **glycine.**
- The bile alcohols (cholane derivatives) of lower animals form esters with sulfuric acid

End of Topic